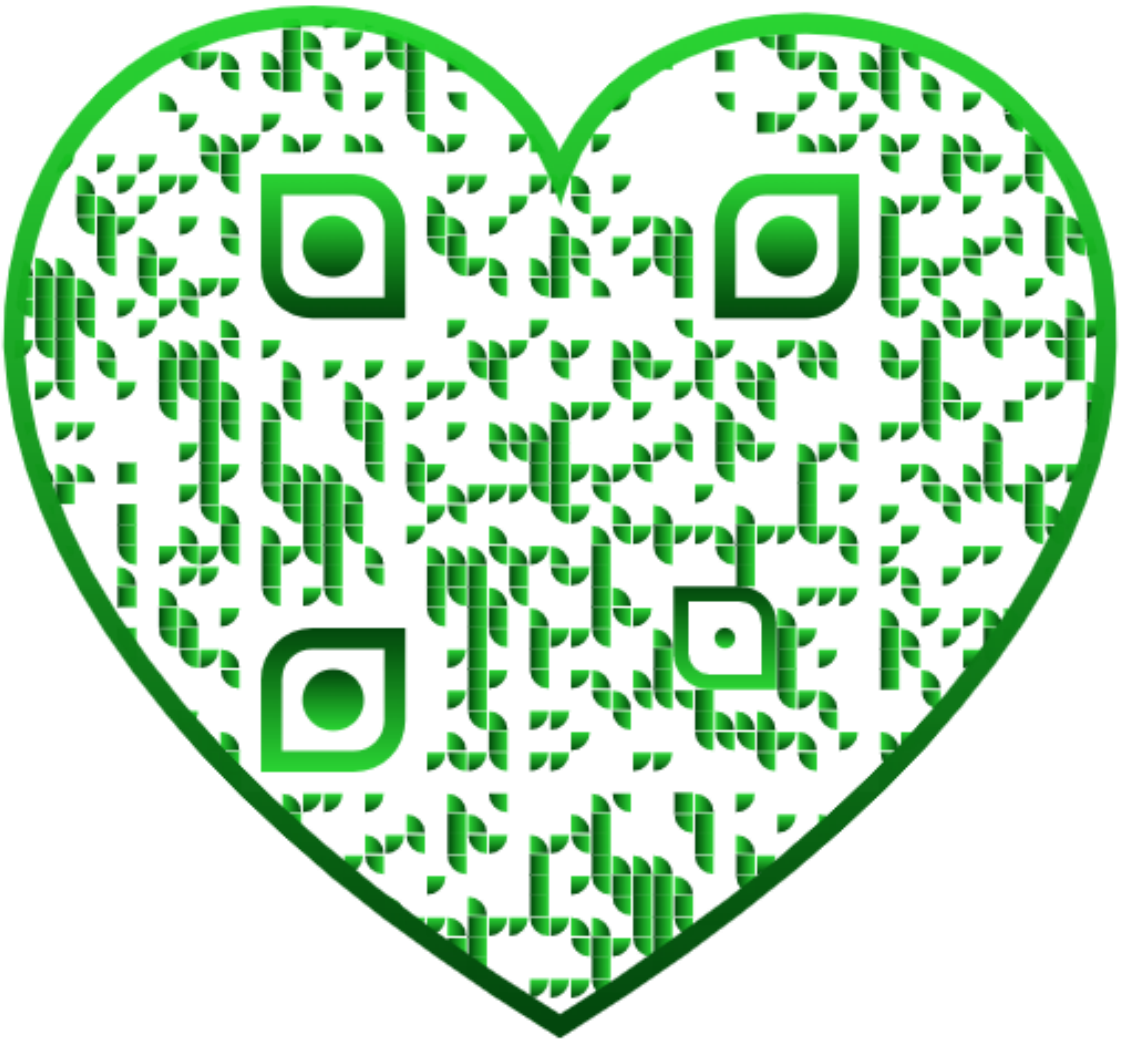
10. Pharmaceutical Emulsions

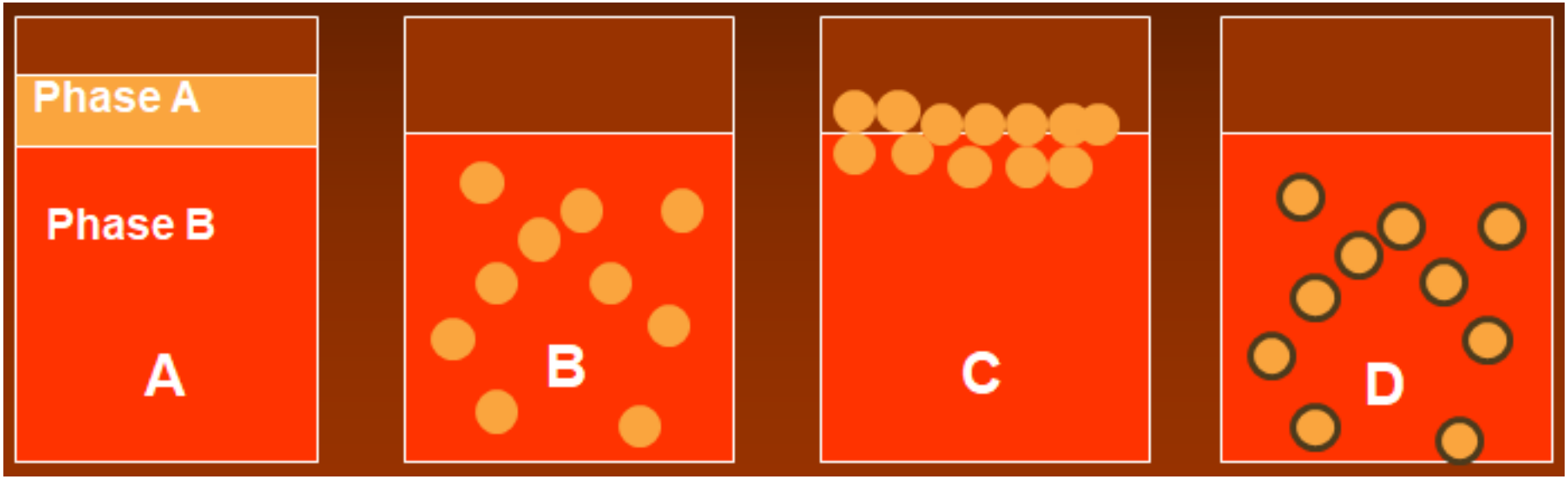


Introduction

Definition:

- A thermodynamically unstable system consisting of at least two immiscible liquid phases,
- One of which is dispersed as globules in the other liquid phase stabilized by a third substance called emulsifying agent.
- The droplet phase is called the dispersed (internal) phase and the liquid in which droplets are dispersed is called the external (continuous) phase.

...



A. Two immiscible liquids not emulsified

B. An emulsion of phase B dispersed in Phase A (unstabilized)

C. Unstable emulsion slowly separates.

D. The emulsifying agent (black film) places it self on the interface between phase A and phase B and stabilizes the emulsion.

Types of Emulsions

- Three categories of emulsions:

1) Simple emulsions (Macro emulsions)
   - Oil-in-water (O/W)
   - Water-in-oil (W/O)
2) Multiple emulsions
   - Oil-in-water-in-oil (O/W/O)
   - Water-in-oil-in-water (W/O/W)
3) Micro-emulsions

...

Oil-in-Water (O/W) Emulsions

- Oil droplets are dispersed in a continuous aqueous phase,
- The globule size is 0.25 to 10 microns.
- The aqueous phase constitutes more than 45 % of the total weight,
- A hydrophilic emulsifier is used,
- Preferred for oral administration and cosmetics (?),
- Useful as water washable drug bases.

...

Water-in-Oil (W/O) Emulsions

- Aqueous droplets are dispersed in continuous oily phase,
- This emulsion is generally formed if the oily phase constitutes more than 45 % of the total weight,
- A lipophilic emulsifier is used,
- These are used for cosmetics (?),
  - The are employed for treatment of dry skin and emollient applications.

Multiple Emulsions

- Usually developed with a view to delay the release of an active ingredient.
- They have three phases: O/W/O or W/O/W
- Various ionic and non-ionic surfactants are used to stabilize the emulsions,
  - Lipophilic (low HLB) surfactants are used to stabilize w/o emulsions,
  - Hydrophilic (high HLB) surfactants are used to stabilize o/w systems

...

- In such emulsions drug present in innermost phase must now cross two phase boundaries to reach the external continuous phase,
- They can undergo inversion:
  - And during inversion they form simple emulsions,
  - So, a w/o/w emulsion will get inverted to o/w emulsion
- Applications:
  - Aimed for slow and SR of active matter from an internal reservoir,
  - Also improve dissolutions or solubilization of insoluble materials,
  - To protecting sensitive and active molecules such as vitamins C and E from the external phase

...

Micro-Emulsions

- Defined as dispersions of insoluble liquids in a second liquid that appears clear and homogenous to the naked eye,
- Believed to be thermodynamically stable (??),
- Referred to as solubilized systems because on a macroscopic basis they seem to behave as true solutions.
- Synonyms: transparent emulsions, micellar solutions, solubilised systems, swollen micelles,
- Globule size ~ below the range of 10-75 nm,

Factors affecting type of Emulsion

- Type of emulsion produced (o/w or w/o) depends upon the following factors:

1) Type of emulsifying agent

2) The phase volume ratio

3) Viscosity of each phase

Determination of Emulsion type

- The following methods can be used to determine type of simple emulsion (O/W or W/O):

1) Dilution test (preferably for liquid emulsions)
2) Dye solubility test
3) Conductivity test
4) $CoCl_2$ filter test (Blue to Pink)
5) Fluorescence test

Pharmaceutical Applications

- Oral products
  - It covers the unpleasant **taste**
  - Increases **absorption** rate
- O/W Parenteral emulsion
  - **IV lipid** nutrients (PNs)
  - **IM-depot** effect for water soluble antigenic material
- Topical use:
  - Washable
  - Acceptable viscosity
  - Less greasy

} **Cosmetically accepted**

Theories of Emulsification

- When two immiscible liquids are mechanically agitated, both phases initially tend to form droplets,
  - When the agitation is stopped, the droplets quickly coalesce, and the two liquids separate (why?),
  - During agitation, formed droplets will have increased SA (and increased interfacial tension),
  - This, in turn, increase the surface energy, and the system becomes thermodynamically unstable,
  - The lifetime of the droplets is materially increased if an emulsifier is added to the two immiscible liquids,

...

- Theories to explain how emulsifying agents promote emulsification:

1) Surface tension theory

  - The use of EAs (surfactants) lowers the interfacial tension, and facilitate formation of globules.

  - By reducing the repellent force between the liquids and diminishing each liquids attraction for its own molecules.

...

2) Oriented – wedge theory

- "Molecular orientation of EAs in surfaces"
- This theory assumes formation of monomolecular layers of SAAs on a droplet of the internal phase,
- Depending on the solubility of the EA in that particular liquid,
- If the non-polar end of the molecule of the EA is smaller, the emulsion will be one of oil in water type.

...

3) Interfacial film theory

- Describes that the SAA is located at the interface between the oil and water,
- Forming a thin film by being adsorbed onto the surface of the internal phase droplets,
- The film prevents the contact and subsequent coalescence of the dispersed phase.
- Stability Vs. Film strength (??)

- Emulsifying agents assist in the formation of emulsions by three mechanisms:
  - Reduction of interfacial tension – thermodynamic stabilization.
  - Formation of a rigid interfacial film – mechanical barrier to coalescence.
  - Formation of an electrical double layer – electrical barrier to approach of particles.

$$\Delta F = 6\gamma \frac{V}{d}$$

- Δ F = surface energy
- γ = interfacial tension
- V = vol. of dispersed phase
- d = diameter of globules

Formulation of Emulsions

Ingredients for the formulation of emulsions

1. Emulsifying agents
2. Auxiliary emulsifiers
3. Antimicrobial preservatives
4. Antioxidants

...

1. Emulsifying agents

- Purpose and mechanism (?)
- Classification of EAs:

1. Synthetic: Surface active agents (Monomolecular films)
2. Semi synthetic and natural: Hydrophilic colloids (Multimolecular films)
3. Finely divided solid particles (Particulate film)

...

- **Synthetic**: Surface active agents (Monomolecular films)

a) Anionic: Soaps, Sulphates, Sulphonates

b) Cationic: Quaternary ammonium compounds

c) Non-ionic

- Polyoxyethylene fatty alcohol ethers
- Sorbitan fatty acid esters
- Polyoxyethylene sorbitan fatty acid esters
- Polyoxyethylene polyoxypopylene block copolymers
- Lanolin alcohols and ethoxylated lanolin alcohols

...

- **Semi synthetic and Natural**: Hydrophilic colloids (Multimolecular films)
  - Provide a protective sheath (Multimolecular films)around the droplets
  - Impart a charge to the dispersed droplets (so that they repel each other)
  - Swell to increase the viscosity of the system (so that droplets are less likely to change)

- **Natural**
  - From plant origin: Polysaccharides (Acacia, tragacanth, agar, pectin, lecithin)
  - From animal origin: Proteins (Gelatin), Lecithin, Cholesterol, Wool fat, Egg yolk
- **Semi synthetic**
  - Methyl cellulose (MC)
  - Carboxymethyl cellulose (CMC)

...

- **Finely divided solid** particles (Particulate film)
  - Solids wetted to some degree by both oil and water act as emulsifying agents.
  - Concentrated at interface, where they produce a particulate film around the dispersed droplets to prevent coalescence
  - Colloidal Clays: Bentonite, Veegum (Magnesium Aluminium silicate), Magnesium trisilicate.
  - Metallic hydroxides: Magnesium hydroxide, Aluminium hydroxide

...

- Ideal emulsifying agent:
  - Reduce the interfacial tension,
  - Physicochemically stable, inert and compatible,
  - Non-irritant and non-toxic in the concentrations used.
  - Organoleptically inert,
  - Form a coherent film around the globules and should prevent the coalescence,
  - Produce and maintain the required viscosity of the preparation

- Factors affecting choice of emulsifying agent:
  - Shelf life of the product
  - Type of emulsion desired
  - Cost of emulsifier
  - Compatibility
  - Non toxicity
  - Taste
  - Chemical stability.

...

2. Auxiliary (Secondary) emulsifiers

- Incapable themselves of forming stable emulsion,
- Their ability to function as thickening agents help to stabilize the emulsion,
- Also provide a physical barrier between droplets,
- Proteins, semisynthetic polysaccharides (MC, CMC), and clays can be used as auxiliary agents

Auxiliary EAs	Use
Cetyl alcohol	Lipophilic thickening agent and stabilizer for o/w lotions and ointments.
Glyceryl mono stearate	Lipophilic thickening agent and stabilizer for o/w lotions and ointments.
Methyl cellulose	Hydrophilic thickening agent and stabilizer for o/w emulsions , weak w/o emulsions.
Sodium CMC	Hydrophilic thickening agent and stabilizer for o/w emulsions ,
Stearic acid	Lipophilic thickening agent and stabilizer for o/w lotions and ointments. Forms a true emulsifier when reacted with alkali.

...

3. Antimicrobial preservatives

a) Acids and acid derivatives: Benzoic acid (Antifungal)

b) Aldehydes: Formaldehyde (Broad spectrum)

c) Phenolics: Phenol, Cresol, Propylhydroxy benzoate (Broad spectrum)

d) Quaternaries: Chlorhexidine and salts, Benzalkonium chloride, Cetyl trimethyl ammonium bromide (Broad spectrum)

e) Mercurials: Phenyl mercuric acetate (Broad spectrum)

...

4. Antioxidants

- Many organic compounds are subject to autoxidation upon exposure to air,
- Emulsified lipids are particularly sensitive to attack,
  - Upon autoxidation, unsaturated oils rancidity with resultant unpleasant odour, appearance, and taste
- Many drugs incorporated into emulsions are also subject to autoxidation,

...

- Commonly used antioxidants:
  - Gallic acid, Propyl gallate: pharmaceuticals and cosmetics (Bitter taste)
  - Ascorbic acid: Suitable for oral use products
  - Sulphites: Suitable for oral use products
  - L-tocopherol: Pharmaceuticals and cosmetics -Suitable for oral preparations e.g. those containing vitamin A
  - Butylated hydroxyl toluene: Pharmaceuticals and cosmetics - Pronounced odor, to be used at low conc.
  - Butylated hydroxylanisol: Pharmaceuticals and cosmetics

Formulation of Emulsions

Chemical Factors Affecting Formulation of Emulsion

1. Purpose
2. Chemical stability
3. Inertness
4. Safety
5. Selection of liquid phase
6. Phase ratio
7. Selection of EA
8. Selection of preservative
9. Selection of antioxidant

Preparation of Emulsions

Emulsification techniques

- Two steps for emulsification:

1) Breaking of internal phase into droplets – by putting energy into the system

2) Stabilization of droplets

...

Extemporaneous (Laboratory scale) method of preparation

1. Continental or dry gum method
2. Wet gum method
3. Bottle or Forbes bottle method
4. Auxiliary method
5. *In situ* soap method

...

Dry gum (Continental) method

- Used to prepare the primary emulsion from oil, water and a hydrocolloid or "gum" type emulsifier (usually acacia),
- The primary emulsion is formed from 4 parts of oil, 2 parts of water and 1 part of gum,
  - 1 part of gum (acacia) is levigated with 4 parts of oil until the powder is thoroughly wetted;
  - Then, 2 parts water is added with vigorous and continuous trituration until the primary emulsion formed
  - Additional water or aqueous solutions may be incorporated

...

Wet gum (English) method

- The proportion remains the same as in dry gum method, but the order and technique of mixing are different,
- The gum is triturated with water to form a mucilage,
- Then oil is slowly added in portions, while triturating,
- After all the oil is added, the mixture is triturated for several minutes to form the primary emulsion,
- Then other ingredients are added as in continental method.

...

Bottle method

- Used to prepare emulsions of volatile oils or oligeneous substances of low viscosities,
- Acacia (or other gum) is placed in a dry bottle and oil is added,
- The bottle is capped and thoroughly shaken (time?), and required volume of water is added,
- Mixture is shaken thoroughly until the primary emulsion is formed,

...

Auxiliary method

- An emulsion prepared by other methods can also be improved by passing it through a hand homogenizer,
- Forcing the emulsion through a very small orifice, reducing the dispersed droplet size to about 5 microns or less.

...

In situ soap method

- Read

...

Large scale method of preparation

- Physical parameters affecting the droplet size distribution, viscosity, and stability of emulsion:
  - Location of the emulsifier,
  - Method of incorporation of the phases,
  - The rates of addition ,
  - The temperature of each phase and
  - The rate of cooling after mixing of the phases considerably

- Energy may be supplied in the form of:
  - Heat
    - Emulsification by vaporization
    - Emulsification by phase inversion
    - Low energy emulsification
  - Homogenization
  - Agitation

- Mechanical stirrers
- Propeller type mixers
  - Turbine mixers
  - Homogenizers
- Colloid mills
- Ultrasonifiers

Mechanical stirrers

Turbine stirrer

Propeller stirrer

Colloidal mill

Colloidal mill rotor and stator

Emulsion stability

Types of instabilities in Emulsions

1. Flocculation
2. Creaming or sedimentation
3. Aggregation or coalescence
4. Phase inversion

...

Flocculation

- Redispersible association of particle within an emulsion to form large aggregates.
- Precursor to the irreversible coalescence,
- Differs from coalescence mainly in that interfacial film and individual droplets remain intact,
- Influenced by the charges on the surface of the emulsified globules

...

Creaming and Sedimentation

- Upward/downward movement of dispersed droplets of emulsion relative to the continuous phase (due to the density difference between two phases),

- Stoke's law?? Vs rate of creaming/sedimentation?

...

Aggregation, Coalescence, Breaking (Cracking)

- Aggregation: Dispersed particles come together but do not fuse.
- Coalescence: is the process by which emulsified particles merge with each to form large particles.
- Breaking: is the destroying of the film surrounding the particles.
- The major factor to prevent coalescence is the mechanical strength of the interfacial film

...

Phase inversion

- An emulsion is said to invert when it changes from an o/w to w/o or vice versa.
- Addition of electrolyte :
- Addition of $CaCl_2$ into o/w emulsion by sodium soaps can be inverted to w/o.
- Changing the phase volume ratio

Emulsion stability

Evaluation of emulsion stability

Stress conditions

1. Thermal stress
   - Aging and temperature
   - Phase inversion temperature
2. Gravitational stress
3. Agitation

Emulsion stability

Evaluation of emulsion stability

Physical parameters

1. Phase separation
2. Viscosity
3. Particle size number analysis
4. Chemical parameters
5. Electrophoretic properties
   - Zeta potential
   - Electrical conductivity
   - Dielectric constant